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Stress-Dependent Association Between Polygenic Risk for Schizophrenia and Schizotypal Traits in Young Army Recruits

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Schizotypal personality traits may increase proneness to psychosis and likely index familial vulnerability to schizophrenia (SZ), implying shared genetic determinants with SZ. Here, we sought to investigate the contribution of common genetic risk variation for SZ on self-reported schizotypy in 2 ethnically homogeneous cohorts of healthy young males during compulsory military service, enrolled in the Athens Study of Proneness and Incidence of Schizophrenia (ASPIS, *N* = 875) and the Learning on Genetics of Schizophrenia Spectrum study (LOGOS, *N* = 690). A follow-up psychometric assessment was performed in a subsample of the ASPIS (*N* = 121), 18 months later at military service completion. Polygenic risk scores (PRS) for SZ were derived based on genome-wide association meta-analysis results from the Psychiatric Genomics Consortium. In the ASPIS, higher PRS_{SZ} significantly associated with lower levels of positive (ie, perceptual distortions), disorganization and paranoid facets of schizotypy, whereas no association with negative (ie, interpersonal) facets was noted. Importantly, longitudinal data analysis in the ASPIS subsample revealed that PRS_{SZ} was inversely associated with positive schizotypy at military induction (stressed condition) but not at follow-up (nonstressed condition), providing evidence for environmental rather than SZ-implicated genetic influences. Moreover, consistent with prior reports, PRS_{SZ} was positively correlated with trait anxiety in the LOGOS and additionally the recruits with higher PRS_{SZ} and trait anxiety exhibited attenuated paranoid ideation. Together, these findings do not support an etiological link between increased polygenic liability for SZ and schizotypy, suggesting that psychosocial stress or trait anxiety may impact schizotypal phenotypic expressions among healthy young adults not genetically predisposed to SZ.

Key words: anxiety/genetic risk/personality/psychosis/psychosocial stress/schizotypy

Introduction

An etiological continuum between schizotypal personality and the development of psychosis, particularly schizophrenia (SZ)-spectrum disorders, has emerged over the past decades.[1] Epidemiological and genetic evidence supports a dimensional relationship between schizotypy and clinical symptomatology reminiscent of SZ,[2] demonstrating that schizotypal features cluster in individuals with elevated risk for SZ and are prodromal to the full-blown clinical manifestation of SZ.[3–5] Furthermore, the manifestation of

schizotypal personality traits has been reported to represent a significant predictor of transition to psychosis later in life.[5] Increased levels of schizotypy are often observed among the biological relatives of patients with SZ,[6,7] suggesting a connection between schizotypal personality and genetic predisposition to SZ, which is likely attributed to overlapping genetic determinants. Prior candidate gene studies have provided some evidence that common genetic polymorphisms associated with SZ may be linked to schizotypy phenotypic variability among healthy individuals,[8–11] further suggesting common genetic underpinnings with SZ. It is also of interest that family-based linkage findings have highlighted a genetic correlation between the diagnosis of SZ and schizotypy in nonpsychotic relatives.[12] In addition, substantial heritability estimates have been reported for psychometrically identified schizotypy in twin-based population studies.[13–15]

Besides a genetic component, several studies have also implicated an environmental impact on schizotypy, which seem to vary depending on the specific schizotypy dimension examined.[16–18] Adverse environmental and psychosocial influences, such as stressful life events, childhood trauma and abuse, social maltreatment from others and peer victimization have been considered important risk factors for the exacerbation of schizotypal features and/or subthreshold psychotic experiences.[19–25] Of note, a nonpathological role for schizotypal personality has been proposed, which does not reflect a genetic vulnerability with SZ and it is related to psychosocial aspects of everyday life or represents a compensatory mechanism of psychosis risk.[26–28] Similarly, positive schizotypy (ie, perceptual distortions) has been associated with a more creative style of living in nonclinical populations,[29–31] supporting the notion that certain schizotypal features do not always denote an alarming or imminent sign of psychopathology, instead they might reveal healthy functioning.[27] It is well documented that schizotypal traits occur among healthy individuals, outlining a continuity of the schizotypy phenotype within the general population.[32–36]

In the current study, we aimed to explore the relationship between common genetic risk variation for SZ, defined as increased loading of genetic risk loci associated with SZ (ie, polygenic risk) through large-scale genome-wide association studies (GWAS) and schizotypal traits in 2 independent cohorts of Greek healthy young males undergoing compulsory military training. Military induction is considered to be associated with increases in subjective stress caused by being away from home, exposure to combat scenarios, sleep deprivation and the rules and regime of initiation into the army corps. A number of studies have shown increased stress levels during the first weeks of military service,[37–40] followed by a subsequent reduction of stress upon leaving the army.[41,42] Therefore, secondary analyses were performed to evaluate the moderating role of environmental stress using a semi-experimental stress exposure paradigm.

Methods

Participants

Athens Study of Psychosis Proneness and Incidence of Schizophrenia. A detailed description of the Athens Study of Psychosis Proneness and Incidence of Schizophrenia (ASPIS) has been previously reported.[19,33,34,43] Briefly, the ASPIS examined randomly selected Caucasian young male conscripts (mean age: 20.8 ± 1.9), during the first 2 weeks of admission to the National Air Force Training Center (Tripolis, Greece). Military service is compulsory in Greece, and all healthy men are recruited and randomly assigned to the different army corps. Within the ASPIS, 8 consecutive separate waves of conscripts underwent psychometric, cognitive, and neurophysiological assessments. A total of $N = 1355$ conscripts successfully completed self-administered questionnaires measuring schizotypal traits at military induction.[34] A follow-up psychometric evaluation was conducted in an ASPIS subsample ($N = 145$) 18 months later, at the completion of military service.[19] We hypothesized that the first 2 weeks of military training represent a period of elevated psychosocial stress (stressed condition), supported by findings of a previous study demonstrating that military service induction resulted in an excess of stress-induced subclinical psychotic experiences in the ASPIS, which were significantly attenuated at military service completion (nonstressed condition).[19] In the current study, we included a total of $N = 875$ eligible individuals who had been genotyped for the purposes of a prior GWAS of neurocognitive functions,[44] and had complete psychometric data. Of those, a subsample of $N = 121$ individuals underwent a follow-up psychometric evaluation. Before participation, all conscripts received a standardized screening interview by a team of military doctors to exclude serious medical conditions, including documented diagnosis of psychotic disorders and substance dependence, and individuals with such conditions were not admitted for military training. Written informed consent was obtained from every individual before enrollment to the study. The research protocol was approved by the Ethics Committee of the University Mental Health Research Institute (Athens, Greece) and the Johns Hopkins University Institutional Review Boards.

Learning on Genetics of Schizophrenia Spectrum. The Learning on Genetics of Schizophrenia Spectrum (LOGOS) represents an independent cohort of healthy young male army conscripts which has been described in detail previously.[45,46] The conscripts participating in the LOGOS did not differ from those of the ASPIS in terms of demographic characteristics (gender, age, years of education, ethnicity), ensuring that

the 2 cohorts are highly comparable to each other and suitable for genetic research and behavioral assessment. The LOGOS acquired the same recruitment procedures as the ASPIS, assessing Caucasian healthy male conscripts (N = 690; mean age: 22.3 ± 3.7) on multiple cognitive and psychometric phenotypes, at the Greek Army Training Camp in Heraklion, Crete, Greece. Following presentation of the study's methods and goals in each consecutive series of new conscripts, every participant willing to volunteer had a detailed information sheet and gave written informed consent. The LOGOS research protocol was approved by the Ethics Committee of the University of Crete, the Executive Army Bureau, and the Bureau for the Protection of Personal Data of the Greek State.

Psychometric Assessment. In the ASPIS, lifetime schizotypal traits were assessed with the Schizotypal Personality Questionnaire (SPQ),[47] and unusual body perceptual experiences with the Perceptual Aberration Scale (PAS),[48] both at the time of military induction and at follow-up. The SPQ is a 74-item questionnaire that includes 9 subscales (Ideas of Reference, Social Anxiety, Odd Beliefs/Magical Thinking, Unusual Perceptual Experiences, Eccentric/Odd Behavior and Appearance, No Close Friends, Odd Speech, Constricted Affect, Suspiciousness/Paranoid Ideation) relevant to schizotypal personality disorder as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R). The factorial structure of the SPQ as defined by the responses of this sample was assessed through confirmatory factor analysis, which indicated that the best fit to the data was provided by a 4-factor model, namely positive, negative, disorganization, and paranoid factors.[34] This 4-factor model of schizotypy has been replicated by other research groups,[49] and importantly high SPQ scores in this sample were predictive of an independent diagnosis of Schizotypal Personality Disorder upon SCID-II clinical interview.[50] The PAS is a 35-item (yes/no) self-rated scale comprised of items tapping unusual perceptual distortions, mainly related to one's own body. PAS total scores showed significant skewness in our population, hence a log-transformation was applied to reach a normal distribution before statistical analysis. Schizotypal traits were assessed with the Schizotypal Traits Questionnaire (STQ) in the LOGOS cohort.[51] The STQ scale is a 37-item self-report questionnaire derived from the criteria for Schizotypal Personality Disorder in the DSM-III and measures 3 dimensions of positive schizotypy, namely unusual experiences, magical thinking, and paranoid ideation. Each item is scored by using a dichotomous (yes/no) response format. Trait anxiety refers to relatively stable individual differences in proneness to anxiety and was assessed with the Spielberger's State-Trait Anxiety Inventory-Trait Scale (STAI-T),[52] which is a 20-item scale and each item is scored on a 4-point Likert scale, ranging from 1 (very false for me) to 4 (very true for me).

Genome-Wide Genotyping. Details on the genotyping procedures, single nucleotide polymorphism (SNP) calling and subsequent quality control (QC) filtering steps acquired by the ASPIS and LOGOS have been previously reported.[44–53] Appropriate postgenotyping QC data cleaning, as well as multidimensional scaling (MDS) or principal components analysis (PCA) to identify genetic outliers and correct for any residual population substructure were performed using PLINK v1.07 and EIGENSTRAT softwares.[54,55] Further information is provided in the supplementary material.

Polygenic Risk Scoring. Polygenic risk scores (PRS) which encompass the additive effect of multiple common SNPs across the genome, were computed based on the GWAS meta-analysis summary results reported by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC),[56] following the procedure originally described by the International Schizophrenia Consortium.[57] Different sets of SNPs were filtered by applying increasing P-value thresholds (P_T < .001, P_T < .01, P_T < .05, P_T < .1, P_T < .3, P_T < .5) to PGC GWAS summary statistics (discovery sample). The same sets of SNPs were extracted in the ASPIS and LOGOS (target samples) (supplementary table S2) and PRS was computed using the "--score" command in PLINK, after appropriate linkage disequilibrium-based SNP pruning (r^2 < .2 within a 200 kb window), ensuring that only independent association signals are included in PRS. For each individual, a weighted score is derived based on the number of risk alleles that the individual carries at each SNP locus, weighted by the natural logarithm of the reported odds ratio for that particular SNP in the reference PGC GWAS. The sum of single scores across all SNPs denotes the total PRS_{SZ} for each individual.

Statistical Analyses

All statistical analyses were performed using R 3.3.2 (https://www.r-project.org/) and SPSS Statistics 23 (IBM). Linear regression analysis was performed to test for associations between quantitative traits scores and PRS_{SZ} at different PGC GWAS P-value thresholds (P_T), including age, years of education and the first two ancestry-based principal components to control for population stratification, as potential confounders. Given the substantial phenotypic correlations between SPQ and PAS scores (Pearson's r > 50) and the lack of independence between PRS_{SZ} computed at different P_T, a conservative Bonferroni correction for multiple comparisons is not preferable, thus statistical significance was determined after a permutation-based resampling procedure (10 000 phenotype permutations were tested) to control

for possible spurious associations. Following permutation testing, empirical *P*-values are reported setting the level of statistical significance at $P < .05$. Separate linear regressions were conducted at baseline (stressed condition) and at follow-up (nonstressed condition), to examine the moderating effect of environmental stress on the association between PRS_{SZ} and schizotypal traits in the ASPIS subsample ($N = 121$). Linear mixed-effects models with repeated measures were fitted to compare the within-subjects phenotypic differences between the 2 conditions, depending on the computed PRS_{SZ}. Each trait was tested with a different model, entering PRS_{SZ} as a fixed effect term, while including each individual as a random effect term (random intercept). Age, years of education, and ancestry-based principal components were included in the model as both fixed and random effects (random slopes). In this longitudinal analysis, the phenotypic differences observed over time between individuals are compared given a specified reference group. Therefore, a dummy variable coding procedure was applied by stratifying the sample based on the median value of the computed PRS_{SZ} at the P_T with the strongest evidence of association. We thus created 2 equally sized groups of individuals (low and high PRS_{SZ} carriers) for further testing, using high PRS_{SZ} carriers as the reference group. For this secondary analysis, uncorrected (nominal) *P*-values are reported. To examine the moderating effect of trait anxiety (STAI-T) on the relationship between PRS_{SZ} and schizotypal dimensions in the LOGOS, multiple linear regression models were carried out including both main effects and 2-way interaction effect terms ($PRS_{SZ} \times$ STAI-T). The Wald χ^2-test was used to determine the statistical significance of the examined interactions, reporting 1-sided tests on the basis of prior evidence from the ASPIS that an inverse relationship between PRS_{SZ} and schizotypy emerged upon stress exposure.

Results

PRS_{SZ} Association With Schizotypal Traits in the ASPIS

In primary analyses, we examined the relationship between PRS_{SZ} derived from 6 different P_T to the PGC GWAS results, the 4 SPQ factor scores (POS: positive, NEG: negative, DIS: disorganization, and PAR: paranoid) and the total PAS score in the ASPIS full sample ($N = 875$) at military induction. All pairwise phenotypic correlations are reported in supplementary table S2. As shown in figure 1, the computed PRS_{SZ} at $P_T < .3$ showed the strongest inverse correlation with SPQ POS ($\beta = -.10$; $R^2(\%) = .96$; nominal $P = .002$; empirical $P = .005$), DIS ($\beta = -.11$; $R^2(\%) = 1.14$; nominal $P = .0008$, empirical $P = .003$), PAR ($\beta = -.09$; $R^2(\%) = .79$; nominal $P = .009$; empirical $P = .01$) and PAS ($\beta = -.10$; $R^2(\%) = .80$; nominal $P = .004$; empirical $P = .017$). In contrast, no statistically significant correlation was observed for SPQ NEG ($\beta = -.05$; $R^2(\%) = .28$; nominal $P = .12$; empirical $P = .11$).

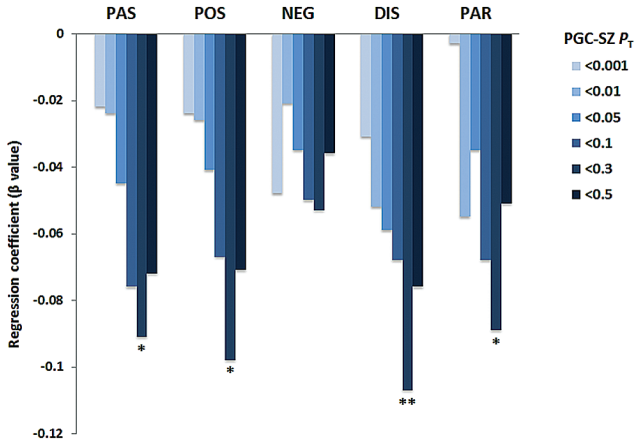

Fig. 1. Association between SPQ factor scores and PRS_{SZ} in the ASPIS full sample ($N = 875$) at military induction (SPQ, Schizotypal Personality Questionnaire; PAS, Perceptual Aberration Scale; POS, SPQ Positive factor; NEG, SPQ Negative factor; DIS, SPQ Disorganization factor; PAR, SPQ Paranoid factor). P_T denotes PGC GWAS *P*-value threshold. $^*P < .01$, $^{**}P < .001$.

Stress-Related Association Between PRS_{SZ} and Positive Schizotypy. We have previously shown that stress exposure during army induction (stressed condition), evoked increases in all SPQ factor scores in the ASPIS, which were alleviated at the end of military service (nonstressed condition).[30] SPQ and PAS mean score reduction in the ASPIS subsample ($N = 121$) at follow-up is shown in supplementary table S3. We intended to test whether environmental stress represents a significant moderator of the observed relationship between schizotypy and PRS_{SZ}. To test the above hypothesis, we first applied separate regression models in the ASPIS subsample, examining the association of PRS_{SZ} (PGC GWAS $P_T < .3$ was utilized which showed the strongest correlation in primary analysis; figure 1) with PAS and SPQ scores in the 2 time points (stressed vs nonstressed conditions). As shown in table 1, a nominally significant association between PRS_{SZ} and PAS was found at stressed condition ($\beta = -.217$; $P = .016$), while a trend association with SPQ POS was also observed ($\beta = -.164$; $P = .065$). However, not such evidence for association was detected at follow-up and the computed effect sizes (regression coefficients) were markedly decreased (PAS $\beta = -.005$; $P = .96$, SPQ POS $\beta = -.004$; $P = .97$). To further verify the above observation and control for potential random effects and phenotypic correlations over time, linear mixed-effects models with repeated measures were performed to determine whether significant differences in PAS/POS scores occurred between stressed and non-stressed conditions among low vs high PRS_{SZ} carriers. We fitted mixed-effects models including a cross-level interaction between the 2

time point and PRS_{SZ}, allowing for the effect of stress (nonstressed condition is the reference) on schizotypy to vary depending on the computed PRS_{SZ} for each individual. Figure 2 depicts the results of the interaction effects (PRS_{SZ} × condition), illustrating higher PAS scores at stressed condition among low PRS_{SZ} carriers compared to high PRS_{SZ} carriers (low PRS_{SZ} mean difference 58.4% vs high PRS_{SZ} mean difference 46.8%, nominal $P = .03$). Similarly, we noted a near significant difference for POS scores (low PRS_{SZ} mean difference 48.7% vs high PRS_{SZ} mean difference 38.4%, nominal $P = .052$). None of the remaining SPQ trait scores showed substantial differences over time (all $P > .2$, supplementary figure S1). Mean phenotypic values for all traits at both conditions, stratified by PRS_{SZ} status, are shown in supplementary table S4.

PRS_{SZ} Predicts Trait Anxiety in the LOGOS. Independent confirmation of the association between PRS_{SZ} and STQ schizotypal traits was attempted in the LOGOS. Additionally, given previous evidence supporting an association between PRS_{SZ} and anxiety symptoms during adolescence,[58] we inquired whether trait anxiety (STAI-T) is also associated with PRS_{SZ} in young conscripts. Moderate pairwise phenotypic correlations were observed between the 3 STQ dimensions and STAI-T (supplementary table S5). Linear regressions were carried out to assess the relationship between PRS_{SZ} and the three STQ dimensions (unusual experiences, magical thinking, paranoid ideation), which revealed that none of the STQ dimensions was significantly associated with PRS_{SZ} ($P > .25$), yet the direction of the correlations was negative in all cases consistent with the ASPIS results. Furthermore, a nominal positive association between PRS_{SZ} and STAI-T was detected at $P_T < .3$ ($\beta = .082$; $P = .05$) and $P_T < .5$ ($\beta = .094$; $P = .03$) (figure 3).

Joint Effect of PRS_{SZ} and Trait Anxiety on Schizotypy. Prompted by the PRS_{SZ} × stress interaction effect observed in the ASPIS, we further explored whether PRS_{SZ} association with STQ dimensions is moderated by trait anxiety in LOGOS. To test the above hypothesis, multiple regression models were fitted for

Table 1. Results From Linear Regression Analysis Depicting the Association Between PRS_{SZ} (PGC $P_T < .3$) and Schizotypal Traits in the ASPIS Subsample ($N = 121$) at Military Induction (Stressed Condition) and at Follow-Up (Nonstressed Condition)

	Stressed Condition		Nonstressed Condition	
Schizotypal Trait	Beta	*P* value	Beta	*P* value
PAS	−.217	**.016**	−.005	.986
POS	−.160	.065	−.004	.998
NEG	.073	.419	−.024	.789
DIS	−.097	.274	−.046	.630
PAR	−.072	.433	−.120	.195

Note: Standardized regression coefficients are reported and nominally significant differences at $P < .05$ (2-sided) are shown in bold. Analyses are controlled for age, years of education, and population stratification principal components. PAS, Perceptual Aberration Scale; POS, SPQ positive factor; NEG, SPQ negative factor; DIS, SPQ disorganization factor; PAR, SPQ paranoid factor.

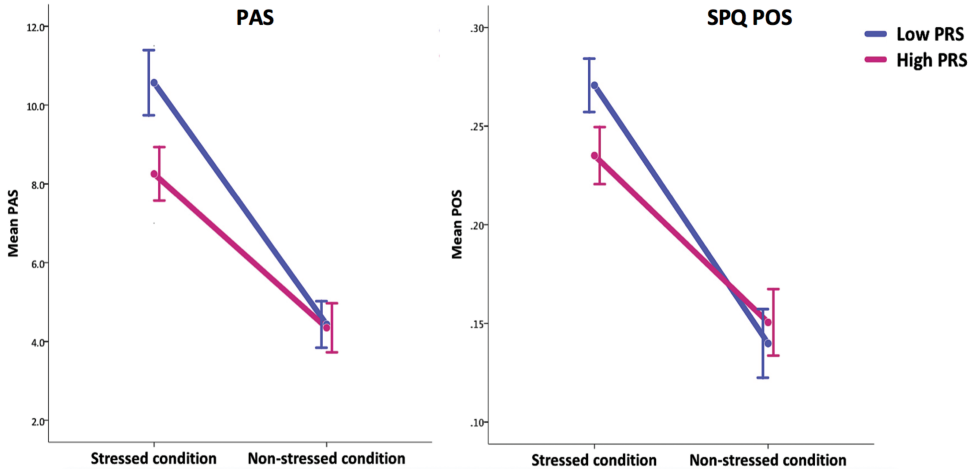

Fig. 2. Mean phenotypic differences for positive schizotypy traits (PAS, SPQ POS) at military induction (stressed condition) and at follow-up (nonstressed condition) in the ASPIS subsample ($N = 121$) stratified by PRS_{SZ} status. Error bars represent the SE of the mean trait scores. PAS $P_{nominal} = .03$, SPQ POS $P_{nominal} = .052$.

each STQ dimension including appropriate 2-way interactions (PRS_{SZ} × STAI-T) as predictors. We noted that the interaction term predicted lower scores for paranoid ideation compared to PRS_{SZ} alone, with substantially increased effect estimates at PRS_{SZ} $P_T < .05$ (β = −.061; 1-sided $P = .026$) and $P_T < .1$ (β = −.057; 1-sided $P = .04$). No statistically significant results were obtained for the unusual experiences and magical thinking STQ dimensions, even though increased regression coefficients were also observed for both traits (PRS_{SZ} $P_T < .05$ β = −.051; 1-sided $P = .064$ for unusual experiences, PRS_{SZ} $P_T < .05$ β = −.056; 1-sided $P = .058$ for magical thinking). Figure 4 illustrates the effect estimates for the association between PRS_{SZ} and STQ dimensions before and after the inclusion of interaction effects with STAI-T scores.

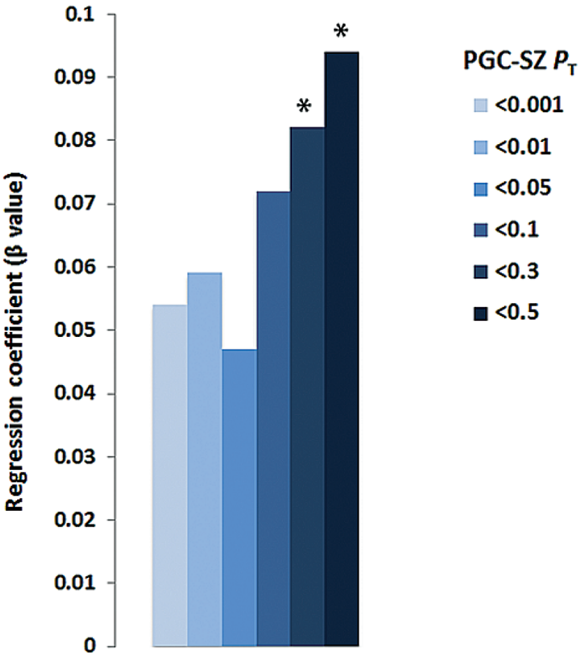

Fig. 3. Association between trait anxiety (STAI-T) and PRS_{SZ} in the LOGOS ($N = 690$) (STAI-T; Trait Scale of the State-Trait Anxiety Inventory). P_T denotes PGC GWAS *P*-value threshold. *$P < .05$.

Discussion

We report findings from 2 population-based cohorts, showing that healthy young males carrying a reduced genetic load of risk alleles for SZ exhibit significantly higher schizotypal traits during compulsory military service. Given that individuals characterized by increased schizotypy or subthreshold psychotic experiences (PEs) may be at a higher genetic risk to develop a psychotic disorder, the inverse association between PRS_{SZ} and schizotypy is somewhat counterintuitive and opposes what would be expected.[4–7] We found that PRS_{SZ} was negatively associated with unusual perceptual experiences, disorganization, and paranoid behavior in the ASPIS during the first 2 weeks of military admission (stressed condition). Follow-up analysis indicated that the observed relationship between PRS_{SZ} and schizotypy was retained at the beginning but not the end of military service (nonstressed condition), likely revealing an environmental impact and not a SZ-related genetic contribution. This finding also suggests pathways of competing genetic and environmental causes rather than genetic and environmental synergism, consistent with a multifactorial threshold model in which genetic predisposition and environmental risk factors influence schizotypy/PEs independently.[59] In addition, a negative correlation between PRS_{SZ} and paranoid behavior was independently observed in the LOGOS and was markedly enhanced when accounting for trait anxiety, further supporting a moderating role for stress/anxiety on the association between PRS_{SZ} and schizotypal personality, at least among young adults.

These findings may offer a tentative explanation for previously reported nonsignificant associations between PRS_{SZ} and PEs in general population samples,[58,60] apparently not exposed to the same levels of environmental stress. Seen from an alternative perspective, these earlier

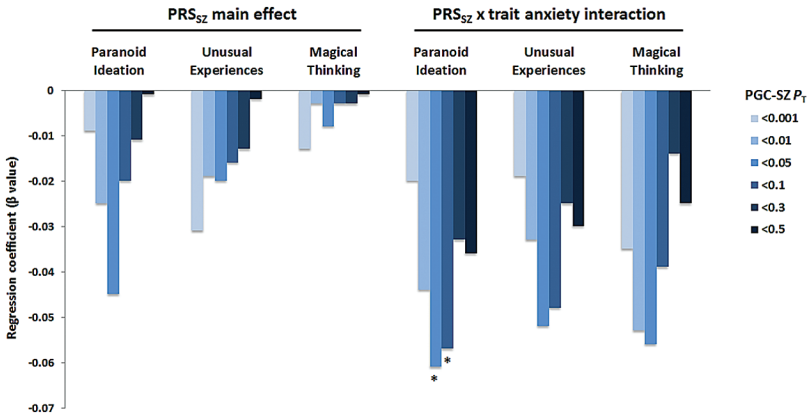

Fig. 4. Associations between STQ dimensions and PRS_{SZ} in the LOGOS before and after accounting for trait anxiety (PRS_{SZ} × STAI-T interaction). STQ; Schizotypy Traits Questionnaire. P_T denotes PGC GWAS *P*-value threshold. *$P < .05$.

studies have observed negative, albeit nonsignificant, correlations between PRS_{SZ} and PEs in children and adolescents, which partially support our findings and imply that the observed associations could not be attributed to trivial phenotype assessment bias (ie, self-ratings of schizotypy) that could have led to spurious results. Indeed, negative associations at trend level between PRS_{SZ} and paranoid behavior as well as cognitive disorganization were previously found among children.[60] In addition, the Avon Longitudinal Study of Parents and Children (ALSPAC) found positive associations between PRS_{SZ} and anxiety disorder incidence in a large sample of adolescents,[58] which is in agreement with the positive correlation between PRS_{SZ} and trait anxiety in the LOGOS.

We postulate that the phenomenological contradictory relationship between PRS_{SZ} and schizotypy could possibly be interpreted in the light of an innocuous phenotypic expression within healthy individuals (ie, healthy schizotypy), which has been originally described by *Jackson* as "benign" schizotypy,[28] and later by *Raine* as "pseudo" schizotypy.[26] Both the above conceptualizations define a personality trait that mostly corresponds to positive schizotypal features and occasionally might prove beneficial, reflecting a relatively healthy expression or coping style which facilitates individuals' adaptation to environmental changes and adversities.[27] It has been reported that this expression of schizotypy has no common neurodevelopmental or genetic origins with SZ and might be triggered by psychosocial factors.[26] The results of this study support the above view, as it may be hypothesized that the occurrence of high genetic risk for SZ among those individuals expressing high schizotypy upon stress exposure, would have possibly caused more detrimental outcomes; for instance the development of a SZ-spectrum psychotic disorder, which defined an exclusion criterion for the current study. Consequently, it is argued that in the nonclinical populations examined in our study, increased schizotypy among low PRS_{SZ} carriers denotes the influence of psychosocial stress and/or anxiety rather than SZ-linked genetic susceptibility, thus supporting the "healthy" schizotypy theoretical framework.[26,28] Likewise, it cannot be assumed that high schizotypy scores specify prodromal signs of psychosis, as higher risk for conversion to psychosis also requires treatment-seeking,[61–63] and risk for SZ is increased primarily in individuals with very high scores who are probably rare in our cohorts.[64,65] It may also be speculated that the lack of polygenic risk for SZ is protective for healthy schizotypes, increasing resilience to psychosis.[1] Further, positive schizotypy measured in healthy individuals does not necessarily resemble a pathological condition; instead it may indicate a compensatory mechanism related to healthy functioning, subjective well-being and creative thinking.[27,66]

Psychosocial stress represents a critical environmental risk factor for psychosis,[67,68] and our group has previously reported that elevated stress levels due to military induction predicted subthreshold PEs in the ASPIS.[69] We would therefore expect that the military environment induces positive schizotypal expressions in the more genetically predisposed recruits carrying higher PRS_{SZ}, however the opposite pattern was observed. An explanation could be derived from the assumption that positive schizotypy reflects an adaptive emotional response to psychosocial stress, in accordance with recent conceptualizations that disengage schizotypy from a linear and unidimensional link to SZ, emphasizing its relevance to affective and social functioning.[70] For example, altered emotional reactivity to stress has been documented in psychotic patients and their first-degree relatives, implying a genetic component to the affective dysregulation observed in psychosis.[71–73] Hence, it is plausible that healthy young adults with relatively increased genetic burden for SZ may also be characterized by a blunted affective response to psychosocial stress (a.k.a. stress reactivity), expressed as reduced positive schizotypy.

In summary, this study challenges the view that the emergence of schizotypal traits in healthy young adults reflects higher genetic liability for SZ and supports an important moderating role for psychosocial stress and trait anxiety. Nevertheless, our results should be interpreted with caution due to a number of limitations. Primarily, both ASPIS and LOGOS comprised limited sized cohorts of young conscripts, who define a distinct population subgroup. The noninclusion of community dwellers, female individuals and individuals of a wider age-range does not allow the generalizability of these findings in the general population. Moreover, the lack of a control (ie, unexposed) condition in our quasi-experimental ASPIS study, specifically a psychometric assessment before the initiation of military service, makes it hard to conclude that army-related psychosocial stress drives the reported associations. It is also acknowledged that the assessment of state anxiety in both cohorts, would ideally confirm the moderating role of environmental stress on schizotypy. Lastly, the use of self-administered instruments to assess personality dimensions may have introduced involuntary phenotypic measurement bias. In order to disentangle the above-mentioned concerns, future studies in larger population-based cohorts are required to establish any relationship between SZ genetic liability and schizotypal personality, as well as to clarify the modifying effects of psychosocial stress and trait anxiety.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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